The npde library for R to compute normalised prediction distribution errors

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Objectives: Over the last few years, several new approaches including VPC (Visual Predictive Check) [1], prediction discrepancies (pd) [2] and normalised prediction distribution errors (npde) [3] have been proposed to evaluate nonlinear mixed effect models. npde are now included in the output of NONMEM [4] and Monolix [5], and we created a R library to facilitate the computation of pd and npde using simulations under the model [6]. We propose a new version of this library with methods to handle data below the limit of quantification (BQL) [7] and new diagnostic graphs [8].

Methods: BQL data occurr in many PK/PD applications, particularly in HIV/HCV trials where multi-therapies are now so efficient that viral loads become undetectable after a short treatment period. These data are generally omitted from diagnostic graphs, introducing biases. Here, we propose to impute the pd for a BQL observation by sampling in $U(0,p_{BQL})$ where p_{BQL} is the model-predicted probability of being BQL. To compute the npde, censored observations are first imputed from the imputed pd, using the predictive distribution function obtained by simulations, then npde are computed for the completed dataset [3].

New graphical diagnostics include a graph of the empirical cumulative distribution function of pd and npde. Prediction intervals, obtained using simulations under the model, can be added to each graph to assess how the distribution of observed data and metrics compare to the expected distribution under the model. Tests can be performed to compare the distribution of the npde relative to the expected standard normal distribution. In addition, graphs and tests to help selecting covariate models have been added [9].

These extensions were implemented in a new version of the npde library. The new library uses S4 classes from R to provide an easier user-interface to the many new graphs, while remaining mostly compatible with the previous version. Exceptions are that computing the pd in addition to the npde is now a default option. Several new options are also available in the computations.

Results: We illustrate the new library on data simulated using the design of the COPHAR3-ANRS 134 trial. In the trial, viral loads were measured for 6 months in 34 naive HIV-infected patients after initiation of a tri-therapy, and up to 50% of data were BQL. Ignoring BQL data results in biased and uninformative diagnostic plots, which are much improved when pd are imputed. Adding prediction intervals is very useful to highlight departures from the model.

Conclusion: Version 2 of the npde library implements a new method to handle BQL data, as well as new graphs, including VPC and prediction intervals for distributions.

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